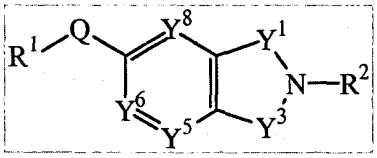
CLAIMS

What is claimed is:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

$(C_1\text{-}C_6$ alkyl)-C(O)O-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl);

$(C_1\text{-}C_6$ alkyl)-N(H)$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)$_2$-$NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl)$_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

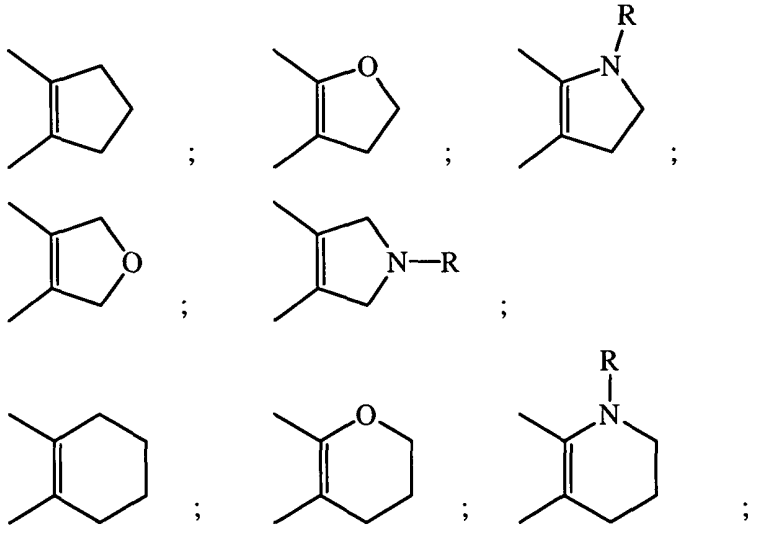
wherein each substituent on a carbon atom may further be independently selected from:

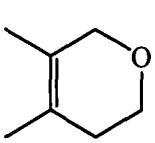
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:

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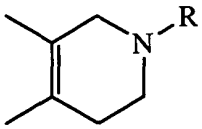
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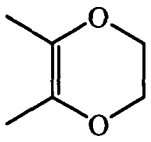
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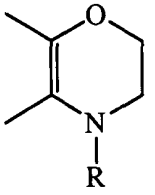
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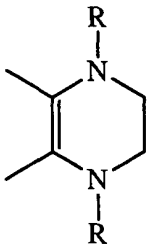
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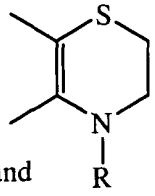
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R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^1 and Y^3 are independently is C(O) or CH_2;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

Q is selected from:

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(S)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

$SC(O)$;

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

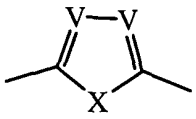
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CCH_2$;

$CF_2C{\equiv}C$; and

$C{\equiv}CCF_2$;



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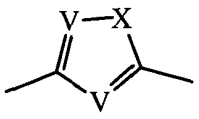

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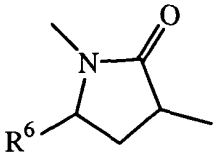

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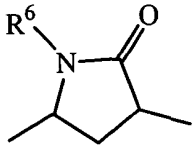

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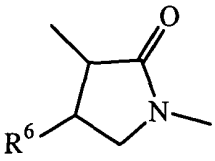

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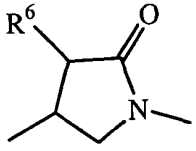

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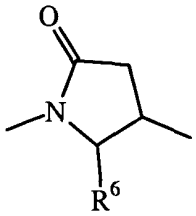

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Each R^6 independently is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V is independently C(H) or N;

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y^5, Y^6, and Y^8 are each $C(R^5)$, wherein each R^5 is independently defined as above.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein one of Y^5, Y^6, and Y^8 is N and the other two of Y^5, Y^6, and Y^8 are each $C(R^5)$, wherein each R^5 is independently defined as above.

4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)C(O)$.

5. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is C≡C.

6. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 and Y^3 are each C(O).

7. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein one of Y^1 and Y^3 is CH_2 and the other of Y^1 and Y^3 is C(O).

8. The compound according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); and

R^2 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl)$_m$;

Substituted phenyl-(C_1-C_8 alkylenyl)$_m$;

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$; and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$;

wherein m is an integer of 0 or 1; and

wherein each group and each substituent is independently selected.

9. The compound according to Claim 1, selected from:

4-[5-(4-Methoxy-benzylcarbamoyl)-1, 3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-benzoic acid;

2-(4-Methanesulfonyl-benzyl)-1,3-dioxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (pyridin-4-ylmethyl)-amide;

2-(3,4-Difluoro-benzyl)-1,3-dioxo-2, 3-dihydro-1H-isoindole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

2-(4-Cyano-benzyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

6-(4-Chloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

6-[2-(4-Cyano-phenoxy)-ethyl]-5,7-dioxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-2-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

2-(4-Chloro-benzyl)-3-oxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

2-(4-Methanesulfonyl-benzyl)-3-oxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (1-methyl-1H-imidazol-2-ylmethyl)-amide;

2-(4-Chloro-3-fluoro-benzyl)-3-oxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;

4-[5-(4-Methoxy-benzylcarbamoyl)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl]-benzoic acid;

2-(4-Cyano-benzyl)-1-oxo-2,3-dihydro-1H-isoindole-5-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

1-Oxo-2-pyridin-4-ylmethyl-2,3-dihydro-1H-isoindole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

2-(4-Methanesulfinyl-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

4-{5-[(Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-1,3-dihydro-isoindol-2-ylmethyl}-benzoic acid; and

2-Pyridin-4-ylmethyl-2,3-dihydro-1H-isoindole-5-carboxylic acid (thiophen-2-ylmethyl)-amide;

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 1, selected from:

4-[1,3-Dioxo-5-(3-phenyl-prop-1-ynyl)-1,3-dihydro-isoindol-2-ylmethyl]-benzoic acid;

2-(4-Methanesulfinyl-benzyl)-5-(3-pyridin-4-yl-prop-1-ynyl)-isoindole-1,3-dione;

2-(3,4-Dichloro-benzyl)-5-(3-imidazol-1-yl-prop-1-ynyl)-isoindole-1,3-dione;

6-(3-Methyl-3-phenyl-but-1-ynyl)-2-(4-methylsulfanyl-benzyl)-pyrrolo[3,4-c]pyridine-1,3-dione;

3-(3,3-Difluoro-3-pentafluorophenyl-prop-1-ynyl)-6-(4-methanesulfonyl-benzyl)-pyrrolo[3,4-b]pyridine-5,7-dione;

2-[3,3-Difluoro-3-(4-fluoro-phenyl)-prop-1-ynyl]-6-(4-methanesulfinyl-benzyl)-pyrrolo[3,4-b]pyridine-5,7-dione;

2-(4-Chloro-benzyl)-6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-2,3-dihydro-isoindol-1-one;

4-{6-[3-(4-Chloro-phenyl)-prop-1-ynyl]-1-oxo-1,3-dihydro-isoindol-2-ylmethyl}-benzenesulfonamide;

2-(4-Chloro-3-fluoro-benzyl)-6-(3-thiazol-3-yl-prop-1-ynyl)-2,3-dihydro-isoindol-1-one;

5-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-2-pyridin-4-ylmethyl-2,3-dihydro-isoindol-1-one;

4-[5-(3-Naphthalen-2-yl-prop-1-ynyl)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl]-benzoic acid;

4-{5-[4-(1H-Imidazol-4-yl)-but-1-ynyl]-1-oxo-1,3-dihydro-isoindol-2-ylmethyl}-N-methyl-benzenesulfonamide; and

4-[5-(3,3-Difluoro-3-phenyl-prop-1-ynyl)-1,3-dihydro-isoindol-2-ylmethyl]-benzoic acid;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

12. The pharmaceutical composition according to Claim 11, comprising a compound according to Claim 9 or 10, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

13. A method for treating osteoarthritis or rheumatoid arthritis, comprising administering to a patient suffering from osteoarthritis or rheumatoid arthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

14. The method according to Claim 13, wherein the compound administered is a compound according to Claim 9 or 10, or a pharmaceutically acceptable salt thereof.